FORMULATION OF CANNABIDIOL IN LIPID CARRIERS

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ABSTRACT

Substances extracted from C*annabis* varieties are of increasing interest, especially cannabidiol as a non-psychoactive drug with various pharmacological effects. Formulation of cannabidiol is, however, challenging due to its low water solubility. In this study, different types of lipid carriers were investigated as formulation options for cannabidiol to enable parenteral or oral application.

The study included self-dispersing lipid formulations, nanoemulsions and liposomes. With regard to parenteral application, a higher load of cannabidiol was obtained in nanoemulsions than in liposomes. Lipid nanoemulsions are thus a very promising formulation option for parenteral formulations with a high drug load. Also in formulations intended for oral use a notably higher amount of cannabidiol could be incorporated in oil-containing self-dispersing formulations than in liposomes.

Keywords: Cannabidiol, lipid carriers, lipid-based formulations

INTRODUCTION

Cannabidiol (CBD) is a natural compound isolated from *Cannabis* varieties which has, unlike Δ^9-tetrahydrocannabinol, not shown psychoactive behaviour [Perez-Reyes, 1973]. Interest in CBD has increased since the beginning of the 2000s and several pharmacological effects are discussed, such as anti-inflammatory, anti-oxidative and neuroprotective action. It is further suggested that CBD might be beneficial in diseases such as Parkinson's disease, diabetes, nausea, cancer, inflammatory diseases and several others [Zuardi, 2008]. How to formulate cannabidiol is therefore an intriguing question in order to enable the use of this promising drug substance. Formulations in lipid carriers are especially promising options due to the lipophilicity of cannabidiol with regard to both parenteral and oral administration. Lipid carriers with sizes in the nanometer range can enable parenteral administration in the therapy with CBD which could be of interest due to the wide field of pharmacological effects. For oral therapy, self-dispersing lipid formulations can be generated using phospholipids as natural emulsifier and solubilizer. These formulations can be filled into hard capsules and disperse in the gastro-intestinal fluids due to mild agitation.

RESEARCH CONCEPT

The maximum amount of drug loaded into dispersed formulations was determined by passive loading, a formulation screening method [Göke, 2017; Rosenblatt 2017]. Using this method, the powdered drug is incubated with the respective carriers in aqueous media and loads into the dispersed carriers by diffusion. The excess of drug is removed from the dispersion by filtration and the amount of loaded drug is analyzed.

For loading experiments with oral formulations, 5 % self-dispersing formulation (38 % medium chain

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triglycerides (MCT), 57 % Phospholipon 90 G, 5 % ethanol 96 %) was dispersed in phosphate buffer pH 7.0. 5 % Phospholipon 90 G was dispersed accordingly to generate liposomes for a comparison. The dispersions were then treated with an ultrasonic probe to reduce the particle sizes to around 200 nm. Centrifugation and subsequent filtration removed titanium particles of the probe and coarse materials from the dispersion. The phospholipid content was then determined by Stewart assay [Stewart, 1980] to check how much lipid was removed by these steps. Briefly, samples were dried under a flow of nitrogen at 40 °C and then dissolved in chloroform. Phospholipids were quantified by colorimetric reaction with ammonium ferrothiocyanate.

Liposomes for parenteral formulations were produced by membrane extrusion. 10 % Lipoid S 75 was dispersed in phosphate buffer pH 7.4 and, after stirring overnight, ten times extruded through a 0.1 µm polycarbonate membrane to achieve a particle size of around 90 nm (all particle sizes were determined by photon correlation spectroscopy).

Emulsions for parenteral application were produced by high-pressure homogenization. The production of the trimyristin emulsion was carried out at 75 °C, all other emulsions were produced at room temperature. Lipid (5 % trimyristin, 10 % MCT or 10 % soybean oil) and aqueous phase (poloxamer 188, sodium azide, water) were weighed in and dissolved separately. Afterwards the phases were united and processed by an ultra-turrax. These pre-emulsions were homogenized ten times in a Microfluidizer. The pressure applied depended on the formulation, resulting mean particle sizes were between 110 nm and 280 nm.

Lipofundin (5 % soybean oil, 5 % MCT, egg phospholipids) is a commercially available parenteral fat emulsion.

Cannabidiol was added to the respective dispersion which was placed on a shaker. In case of oral formulations, samples were drawn in several intervals and analyzed for drug content by UV spectroscopy at 215 nm (solute tetrahydrofuran/acetonitrile (8/2)) until saturation. Lipid carriers for parenteral application were incubated in independent vials and the drug content was analyzed by UV spectroscopy at 212 nm (solute tetrahydrofuran/water (9/1)).

RESULTS

Cannabidiol showed a remarkably high drug load in lipid formulations (up to approx. 47 % in relation to the lipid content (Fig. 1)).

In formulations for oral application, CBD was loaded to a significantly higher extent into the self-dispersing mixture than into liposomes. In parenteral formulations, the trimyristin emulsion showed a considerably higher CBD load compared to emulsions of other oils. Drug loading into the phospholipid- and thus charge-stabilized Lipofundin emulsion led to a comparable drug concentration as for a sterically(poloxamer)-stabilized MCT emulsion. In the same manner as for oral formulations, cannabidiol reached a much higher concentration in all emulsions as compared to liposomes.

DISCUSSION

The very high drug load in the trimyristin emulsion indicates a lipid dependence of achievable CBD load in emulsions. This is in agreement with literature reports, where lipid dependence is also shown for other drugs [Göke, 2017]. A comparable drug load in the differently stabilized Lipofundin and MCT emulsion implicates that there is no strict preference of CBD for sterically or charge-stabilized emulsions. Higher drug loading in emulsions and self-dispersing mixtures compared with liposomes emphasizes an advantage of oil-containing carrier systems for the formulation of CBD.

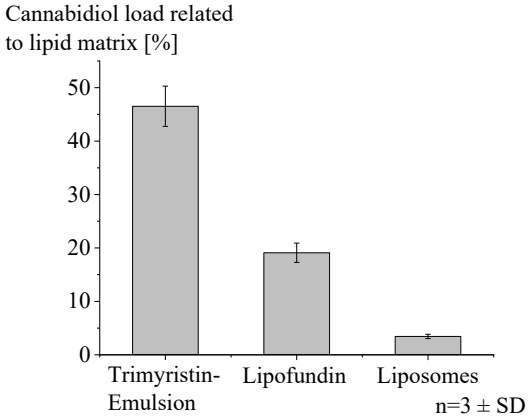

Fig. 1: Drug load of cannabidiol in parenteral formulations.

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CONCLUSIONS

Lipid nanoemulsions achieve a high load of cannabidiol and therefore enable parenteral administration. Due to the lipid-dependent drug loading, the choice of the lipid has to be taken into account upon formulation of CBD in nanoemulsions. Self-dispersing mixtures are a promising option as well, as they facilitate oral administration and can be loaded with high CBD concentrations, too. Liposomes are a less interesting option for CBD formulation as notably less drug substance loaded into these carriers.

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REFERENCES

[Göke, 2017] Göke, K., Bunjes, H., 2017, Drug solubility in lipid nanocarriers: Influence of lipid matrix and available interfacial area, *International Journal of Pharmaceutics*, Vol. 529, 1-2, pp. 617–628.

[Perez-Reyes, 1973] Perez-Reyes, M., Timmons, M. C., Davis, K.H. and Wall, E.M., 1973, A comparison of the pharmacological activity in man of intravenously administered Δ^9-tetrahydrocannabinol, cannabinol, and cannabidiol, *Experientia*, Vol. 29, pp. 1368-1369.

[Rosenblatt, 2017] Rosenblatt K. M., Bunjes, H., 2017, Evaluation of the drug loading capacity of different lipid nanoparticle dispersions by passive drug loading, *European Journal of Pharmaceutics and Biopharmaceutics*, Vol. 117, pp. 49–59.

[Stewart, 1980] Stewart, J. C. M., 1980, Colorimetric determination of phospholipids with ammonium ferrothiocyanate, *Analytical Biochemistry*, Vol. 104, 1, pp. 10–14.

[Zuardi, 2008] Zuardi, A. W., 2008, Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action, *Revista Brasileira de Psiquiatria*, Vol. 30, pp. 271-280

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